b) a labelled first binding partner which binds to the protein in a manner dependent on the conformational state of the protein and is detectable in a manner dependent on its binding to the protein and a labelled second binding partner which binds to the protein in a manner independent of the conformational state of said protein and which is detectable in a manner dependent on the binding of the first binding partner to the protein, wherein said protein and said first binding partner or said second binding partner are not covalently bound,; and

c) packaging components.

REMARKS

Claims 1, 2, 4-8 and 10-22 are currently pending in the application. Claims 1, 2, 3, 19 and 20 are amended. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

Continued Prosecution Application

Applicants note that the request filed on 9/23/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/511,776 is acceptable and a CPA has been established.

Amendment Entry

Applicants gratefully note that Applicant's amendment and response filed 5/30/02 in Paper No. 13 is acknowledged and has been entered by the examiner.

Prior Art

Applicants acknowledge the Examiner's Statement that "Claims 1,4-8 and 10-14, are clear of the prior art of record".

Rejections Withdrawn

Applicants note that the following rejections are withdrawn: the rejection of claims 1, 4-8, and 12-13 under 35 U.S.C. 102(e) as being anticipated by Prusiner et al. (US 5,891,641); the rejection of claims 1, 4-8, and 12-13 under 35 U.S.C. 102(e) as being anticipated by Martinez et al. (WO 98/41872); the rejection of claims 1, 7-8, and 10-11 under 35 U.S.C. 102(e) as being anticipated by Tsien et al. (US 5,998,204); the rejection of claims 19-22 under 35 U.S.C. 03(a) as being unpatentable over Martinez et al. (WO 98/41 872) or Tsien et al. (US 5,998,204) in view of Foster et al. (US 4,444,879); and the rejection of claims 2 and 14 under 35 U.S.C. 103(a) as being unpatentable over 1) Prusiner et al. (US 5,891,641) or Martinez et al. (WO 98/41872) and 2) Tsien et al. (US 5,998,204) in view of 3) Eberwine et al. (WO 96/05847) and 4) Epps et al. (US 6,203,994) or Kinjo et al. (Nucleic Acids Research, 1995).

Rejection of Claims 1-2, 4-8 and 10-14 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-2, 4-8, and 10-14 are rejected under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness.

Claim 1

The Examiner stated that claim 1, step a) is vague and indefinite in reciting, "which can generate a signal in a manner dependent on the binding of the first binding partner to the protein" because in reciting, "can", it fails to recite a positive limitation in the claim.

Applicants have amended claim 1 to replace the phrase "can generate" with the word "generates."

Claim 2

The Examiner stated that claim 2, step b) is vague and indefinite in reciting, "which can generate a signal in a manner dependent on said post-translational modification" because in reciting, "can", it fails to recite a positive limitation in the claim.

Applicants have amended claim 2 to replace the phrase "can generate" with the term "generates."

Claim 13

In response to the Examiner's assertion that claim 13 is indefinite because it appears grammatically redundant in reciting, "removing unbound labelled first binding partner is removed to allow ...", Applicants have amended claim 13 to delete the phrase "is removed" to correct the redundancy.

In view of all of the above, Applicants respectfully request withdrawal of the 35 U.S.C. § 112 second paragraph rejection of claims 1-2, 4-8 and 10-14.

Rejection of Claims 1, 4-8, 10-14 and 19-22 Under 35 U.S.C. § 112, First Paragraph

Claims 1,4-8, 10-14, and 19-22 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of written description.

The Examiner stated that "the specification does not appear to provide any literal or descriptive support for the recitation of 'a labelled second binding partner which binds to said protein in a manner dependent on the conformational state of said protein and which can generate a signal in a manner dependent on the binding of the first binding partner to the protein' and 'a second labelled binding partner ... which can generate a signal in a manner dependent on said post-translational modification'." The Examiner also stated that "none of the originally filed claims recited the limitation in question" and that "recitation of claim limitation lacking literal support in the specification or originally filed claims constitutes new matter". Applicants respectfully disagree.

Applicants submit that claim 1 has been amended to claim "a labelled second binding partner which binds to said protein in a manner **independent** of the conformational state of said protein". (Emphasis added) Support for the amendment is found throughout the specification, for example, at page 7, lines 24-27, wherein the specification states, "[p]referably, the second binding partner does not bind in a strictly conformation-dependent manner, but is capable of

binding to a subset of possible conformations, or even substantially all conformations, of the protein." Applicants submit further that in view of this amendment, the Examiner's rejection of claim 1 for alleged lack of written description for the phrase "a labelled second binding partner which binds to said protein in a manner dependent on the conformational states of said protein" is rendered moot.

The Examiner states that the specification does not provide literal or descriptive support for the recitation of "a labelled second binding partner which binds to said protein in a manner dependent on the conformational state of said protein and **which can generate a signal in a manner dependent on the binding of the first binding partner to the protein**". (Emphasis added) Applicants respectfully disagree.

There is no such requirement of literal support for claim limitations. The Manual of Patent Examining Procedure (MPEP) discusses the standard and procedure for determining compliance with the written description requirement. It states that "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.' " (MPEP § 2163.02, quoting *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989) The MPEP also states that in successfully showing possession of the invention, "[t]he subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." (MPEP, § 2163.02, emphasis added).

Applicants submit that a labelled second binding partner which binds to a protein and which generates a **signal in a manner dependent on the binding of the first binding partner to the protein** is clearly described in the instant application.

The instant application teaches that the first and second binding partners of the invention can be fluorescently labelled and that the binding of the binding partners to the protein is assayed by a number of methods including fluorescence resonance energy transfer (FRET), fluorescence correlation spectroscopy (FCS) and fluorescence anisotropy.

The specification states at page 7, lines 13-16, "both the first and second binding partners may be labelled, and the labels detected by FRET. As described below, FRET occurs between two fluorescent labels which fluoresce in close proximity with each other. Thus, the binding of the binding partner(s) to the protein will be detectable as a result of FRET."

The specification also teaches that FRET detection of a protein conformation encompasses a first and second binding partner, wherein a labelled second binding partner binds to a protein and generates a signal in a manner dependent on the binding of the first binding partner to the protein (see p. 7, lines 13-16, recited above, and the section entitled, "Generation of a Detectable Signal", beginning on p. 18, line 15). The specification states at page 18, lines 27-31, "[s]ince the rate of energy transfer is inversely proportional to the sixth power of the distance between the donor and acceptor, the energy transfer efficiency is extremely sensitive to distance changes. Energy transfer is said to occur with detectable efficiency in the 1-10nm distance range, but is typically 4-6 nm for favourable pairs of donor and acceptor."

The specification describes FCS at p. 22, lines 7-16, wherein the specification states, "a focused laser beam illuminates a very small volume of solution...which at any given point in time contains only one molecule of the many under analysis. The diffusion of single molecules through the illuminated volume, over time, results in bursts of fluorescent light as the labels of the molecules are excited by the laser...a labelled molecule will diffuse at a slower rate if it is large than if it is small."

The specification describes fluorescence anisotropy at p. 22 and the specification states, at p. 28-30, "[f]luorescence anisotropy relies on the measurement of the rotation of fluorescent groups. Larger protein rotate more slowly than smaller binding partners, allowing the formation of protein:binding partner associations to be monitored."

Even in the absence of Applicants' specification, a person of ordinary skill in the art would understand that FRET, FCS and fluorescence anisotropy signal generation is dependent on the proximity of the donor and acceptor fluorescent moieties and the interaction of the donor and acceptor fluorescent moieties. A person of ordinary skill in the art would also understand that

the proximity of the binding partners is dependent on protein conformation and that protein conformation may be dependent on post-translational modification (discussed below).

In view of the above, Applicants submit that a labelled second binding partner which binds to a protein and which can generate a signal in a manner dependent on the binding of the first binding partner to the protein, as claimed in claim 1 and dependent claims 4-8 and 10-14 is adequately described in the specification and that this description clearly meets the legal requirements for 35 U.S.C. 112, § first paragraph.

The Examiner states that the specification does not provide literal or descriptive support for the recitation of "a second labelled binding partner ... **which can generate a signal in a manner dependent on said post-translational modification**". Applicants respectfully disagree. (Emphasis added)

Amended claim 2 and dependent claims 4-8 and 10-14 include the language "a second labelled binding partner which binds non-covalently to said protein and which generates a signal in a manner dependent on said post-translational modification." Applicants assume that the Examiner's failure to include claim 2 in the list of claims rejected under 35 U.S.C. § 112, first paragraph was an oversight.

Applicants submit that the specification states at p. 10, lines 17-18, "[c]onformational change may moreover be induced by post-translational modification of a protein", and includes a list of examples of post-translational modification-inducing conformational changes including phosphorylation of an ion channel and phosphorylation of a receptor signaling protein."

Applicants submit further that Examples 2 and 3 of the specification teach a second labelled binding partner "which can generate a signal in a manner dependent on a post-translational modification". Example 2 discloses using the claimed method of claim 2 to detect conformational changes in p47phox induced by phosphorylation. Example 3 discloses using the claimed method of claim 2 to detect conformational changes in Src kinase induced by phosphorylation.

In view of the above, Applicants submit that a labelled second binding partner which binds to a protein and which can generate a signal in a manner dependent on post-translational modification, as claimed in claim 2 and dependent claims 4-8 and 10-14 is adequately described in the specification and that this description clearly meets the legal requirements for 35 U.S.C. 112, § first paragraph.

Applicants respectfully assert that 'a labelled second binding partner which binds to said protein in a manner dependent on the conformational state of said protein and which can generate a signal in a manner dependent on the binding of the first binding partner to the protein' and 'a second labelled binding partner ... which can generate a signal in a manner dependent on said post-translational modification'." is not recited in claims 19-22. Applicants respectfully request that Examiner clarify why these claims were included in the 35 U.S.C. § 112, first paragraph rejection.

In view of all of the above, Applicants respectfully request withdrawal of the 35 U.S.C. § 112, first paragraph rejections of claims 1, 4-8, 10-14 and 19-22.

Rejection of Claims 1, 4-8, 10-14 and 19-22 For Double Patenting

Claims 1,4-8, 10-14 and 19-22 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 and 18-21 of copending Application No. 09/258,452. The Examiner states that although the conflicting claims are not identical, they are not patentably distinct from each other.

In response to this rejection, Applicants submit that they will submit a terminal disclaimer to disclaim any portion of a patent issuing from the present application which would extend beyond the term of any application issuing from co-pending Application No. 09/258,452, upon notification of allowable claims in the present application.

Rejections of Claims 19-22 Under 35 U.S.C. § 103(a)

Claims 19-22 are rejected under 35 U.S.C. § 103(a) for alleged unpatentability over Prusiner et al. (US 5,891,641) in view of Foster et al. (US 4,444,879).

For the reasons described below, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness under the requirements of 35 U.S.C. § 103(a). To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). Second, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicants' disclosure. Finally, the prior art reference (or references when combined) must teach or suggest *all the claim limitations*. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

The Examiner states that "Prusiner et al. differ from the instant invention in failing to incorporate the protein standards, binding partners, labels, and packaging components into a kit format." and that "Foster et al. disclose controls, reagents including antibodies and labels, and instructions in a kit format for use in assay methods." The Examiner concludes that "It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have incorporated the protein standards, binding partners and label reagents taught by Prusiner into a kit format as taught by Foster et al., for use in a method of determining the conformational state of a protein because kit formats are recognized for their advantage in convenience and economy." Applicants respectfully disagree.

The present Office Action and the previous Office Actions (mailed June 7, 2001 and November 27, 2001) state that Prusiner *et al.* discloses "a method for determining a diseased related conformational state of a protein such as PrP^{Sc} in a sample", and that this reference accomplishes this by "contacting the protein with a labelled antibody that binds (has higher binding affinity) to the protein in a manner dependent on the conformational state of the protein", that is, a diseased or a non-diseased state, and "contacting the protein with a second antibody or capture ligand to immobilize the protein on a solid phase substrate" (column 4, lines 5-10).

Applicants note that this characterization is not precisely correct. Rather, this and another section of Prusiner et al. (column 1, line 65 to column 2, line 20) state that in the assay, the sample is divided into two portions. The first portion is bound to a solid support and then labelled with an antibody that binds to the normal (*i.e.*, non-diseased) form of the protein. The antibody is such that it binds with a higher binding affinity to normal proteins rather than diseased proteins. The second portion of the sample is then treated to cause the diseased proteins to relax into a non-diseased conformation. This treated second portion of the sample is then also bound to a support substrate, and then treated with the same antibody. Whether or not proteins of the diseased form are in the original sample, and to what extent they are present, is determined by assaying the level of antibody binding in the first portion versus the second portion. That is, greater binding of the antibody in the second portion relative to the first portion indicates the existence in the sample of proteins in the diseased state form.

Prusiner *et al.* do disclose "contacting the protein with a second antibody or capture ligand" as is indicated in the Office Action, nor is such a second antibody or capture ligand necessary "to immobilize the protein on a solid phase substrate". Prusiner et al. do not teach or suggest a "labelled first binding partner which binds to the protein in a manner dependent on the conformational state of the protein and is detectable in a manner dependent on its binding to the protein and a labelled second binding partner which binds to the protein in a manner independent of the conformational state of said protein and which generates a signal in a manner dependent on the binding of the first binding partner to the protein, wherein said protein and said first binding partner and said second binding partner are not covalently bound" as claimed in claim 19-22.

Neither Prusiner *et al.* nor Foster *et al.* alone or in combination, provide the elements of Applicants' claims, let alone rendering the invention obvious. Prusiner *et al.* does not teach or suggest both a first binding partner, in which the labelled binding partners binds in a way that is dependent on the protein's conformational state, and a second labelled binding partner, in which the labelled binding partners binds in a way that is independent of the protein's conformational state. Foster *et al.* does not remedy this deficiency. Furthermore, even if Prusiner *et al.* did teach Applicants' first and second binding partners, Prusiner *et al.* does not provide any

motivation to use Applicants' first and second binding partners in a kit. Neither Prusiner *et al.* nor Foster *et al.* provide any motivation to use Applicants' first and second binding partners in a kit. Applicants respectfully request that the rejection be reconsidered and withdrawn.

In view of all of the above, Applicants respectfully request withdrawal of the 35 U.S.C. 103(a) rejections of claims 19-22.

Applicants submit that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention.

Respectfully submitted,

Date: March 17, 2003

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MARKED-UP VERSION OF AMENDMENTS:

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

Please amend claims 1, 2, 13, 19 and 20 as follows:

1. (Three Times Amended) A method for determining the conformational state of a protein, comprising the steps of:

   a) contacting a protein with a labelled first binding partner which binds to said protein in a manner dependent on the conformational state of said protein and which generates a signal in a manner dependent on the binding of the first binding partner to the protein, and a labelled second binding partner which binds to said protein in a manner [dependent on] independent of the conformational state of said protein and which [can generate] generates a signal in a manner dependent on the binding of the first binding partner to the protein, wherein said protein and said labelled first and second binding partner are not covalently bound; and

   b) detecting said protein by the binding of at least one of said labelled first binding partner or said labelled second binding partner to said protein wherein detection of a signal generated by said labelled first binding partner and/or said labelled second binding partner is an indicator of the conformational state of said protein.

2. (Three Times Amended) A method for measuring the post-translational modifying activity of an enzyme, wherein the conformation of a protein is dependent upon the post-translational modification activity of the enzyme, the method comprising the steps of:

   a) contacting a protein comprising a site for post-translational modification with the enzyme;

b) providing a labelled first binding partner which binds non-covalently to the protein in a manner dependent on the post-translational modification of the protein by the enzyme and which generates a signal in a manner dependent on said post-translational modification, and a second labelled binding partner which binds non-covalently to said protein and which [can generate] generates a signal in a manner dependent on said post-translational modification;

c) contacting the protein with the labelled first binding partner and the labelled second binding partner and detecting said protein by the binding to said protein of at least one of said labelled first binding partner and said labelled second binding partner, wherein detection of a signal generated by said labelled second binding partner and/or said labelled second binding partner indicates the post-translational modifying activity of the enzyme.

13. (Three Times Amended) The method of claim 1 or 2, further comprising the additional step of, after step (a), removing unbound labelled first binding partner [is removed] to allow detection of the binding of the labelled first binding partner to the protein.

19. (Twice Amended) A kit for the determination of the conformational state of a protein in a sample, comprising:

a) a labelled first binding partner which binds to the protein in a manner dependent on the conformational state of the protein and is detectable in a manner dependent on its binding to the protein and a labelled second binding partner which binds to the protein in a manner independent of the conformational state of said protein and which generates a signal in a manner dependent on the binding of the first binding partner to the protein, wherein said protein and said first binding partner [or] and said second binding partner are not covalently bound; and

b) packaging components.

20. (Twice Amended) A kit for the determination of the presence of a ligand for a protein in a sample, comprising:

a) a protein which binds to the ligand the presence of which is to be determined and which undergoes a conformational change as a result of such binding;

b) a labelled first binding partner which binds to the protein in a manner dependent on the conformational state of the protein and is detectable in a manner dependent on its binding to the protein and a labelled second binding partner which binds to the protein in a manner independent of the conformational state of said protein and which is detectable in a manner dependent on the binding of the first binding partner to the protein, wherein said protein and said first binding partner or said second binding partner are not covalently bound,; and

c) packaging components.